Sox9-haploinsufficiency causes glucose intolerance in mice.

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Public Summary:
The HMG box transcription factor Sox9 plays a critical role in progenitor cell expansion during pancreas organogenesis and is required for proper endocrine cell development in the embryo. Based on in vitro studies it has been suggested that Sox9 controls expression of a network of important developmental regulators, including Tcf2/MODY5, Hnf6, and Foxa2, in pancreatic progenitor cells. Here, we sought to: 1) determine whether Sox9 regulates this transcriptional network in vivo and 2) investigate whether reduced Sox9 gene dosage leads to impaired glucose homeostasis in adult mice. Employing two genetic models of temporally-controlled Sox9 inactivation in pancreatic progenitor cells, we demonstrate that contrary to in vitro findings, Sox9 is not required for Tcf2, Hnf6, or Foxa2 expression in vivo. Moreover, our analysis revealed a novel role for Sox9 in maintaining the expression of Pdx1/MODY4, which is an important transcriptional regulator of beta-cell development. We further show that reduced beta-cell mass in Sox9-haploinsufficient mice leads to glucose intolerance during adulthood. Sox9-haploinsufficient mice displayed 50% reduced beta-cell mass at birth, which recovered partially via a compensatory increase in beta-cell proliferation early postnatally. Endocrine islets from mice with reduced Sox9 gene dosage exhibited normal glucose stimulated insulin secretion. Our findings show Sox9 plays an important role in endocrine development by maintaining Ngn3 and Pdx1 expression. Glucose intolerance in Sox9-haploinsufficient mice suggests that mutations in Sox9 could play a role in diabetes in humans.

Scientific Abstract:
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